REMARKS

Claims 1-32 have been cancelled. Claims 33-41 are pending.

In response to the Notice of Non-Compliance, Applicants have renumbered the claims previously submitted, beginning with independent claim 33. Dependent claims 34-41 depend from claim 33. The present claims are similar to the claim filed on December 19, 2003, and thus are believed to be within the original restriction requirement.

With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Interview Summary

Applicants respectfully thank the Examiner for the telephonic interview of August 5, 2005, during which the present application was discussed.

Rejection under 35 USC §112, second paragraph and the Double Patenting Rejection

Applicants again thank the Examiner for withdrawing the rejection under 35 USC §112, second paragraph and the Double Patenting rejection.

Rejections under 35 U.S.C. § 101

Claim 1 is rejected under 35 U.S.C. § 101 for lacking a specific asserted utility or a well established utility. In rejecting claim 1, the Examiner's position appears to be that the claimed method generates a secondary library of undefined structure that is so general as to lack a real-world utility. The rejection is moot as applied to cancelled claim 1. Applicants respectfully submit that this rejection does not apply to newly added claims 33-41 for the following reasons.

Newly added claims 33-41 are directed to methods of generating second libraries of variants using a computational step.

The Examiner's basic position appears to be that there is no "specific and substantial utility", citing *In re Kirk*. As a preliminary matter, the Applicants first note that *In re Kirk* is a case dated prior to the new Utility Guidelines, and secondly that *Kirk* is directed to compositions of a new chemical class with a sole utility of "useful biological properties".

As to the first point, the Applicants respectfully draw the Examiner's attention to the Utility Guidelines:

In most cases, an applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101. As the CCPA stated in In re Langer:

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

Thus, Langer and subsequent cases direct the Patent Office to presume that a statement of utility made by an applicant is true. For obvious reasons of efficiency and in deference to an applicant's understanding of his or her invention, when a statement of utility is evaluated, Patent Office personnel should not begin an inquiry by questioning the truth of the statement of utility. Instead, any inquiry must start by asking if there is any reason to question the truth of the statement of utility. This can be done by evaluating the logic of the statements made, taking into consideration any evidence cited by the applicant. If the asserted utility is credible (i.e., believable based on the record or the nature of the invention), a rejection based on "lack of utility" is not appropriate. Thus, Patent Office personnel should not begin an evaluation of utility by assuming that an asserted utility is likely to be false, based on the technical field of the invention or for other general reasons.

Compliance with § 101 is a question of fact. Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, Patent Office personnel must establish that it is more likely than not that one of ordinary skill in the art would doubt (i.e., "question") the truth of the statement of utility. To do this, Patent Office personnel must provide evidence sufficient to show that a person of ordinary skill in the art would consider the statement of asserted utility "false". A person of ordinary skill must have the benefit of both facts and reasoning in order to assess the truth of a statement. This means that if the applicant has presented facts that support the reasoning used in asserting a utility, Patent Office personnel must present countervailing facts and reasoning sufficient to establish that a person of ordinary skill would not believe the applicant's assertion of utility (MPEP §2107.02IIIA). The initial evidentiary standard used during evaluation of this question is a preponderance of the evidence (i.e., the totality of facts and reasoning suggest that it is more likely than not that the statement of the applicant is false). It is respectfully submitted that the Examiner has not met this burden.

The claims are directed to specific methods of computationally generating libraries of proteins. As has been argued previously, these methods have a "real world" utility, as evidenced in several ways. First of all, a "real world" use has been shown because methods of protein design related to those of the present invention have been shown to work as claimed. See also U.S. Patent Nos. 6,188,965; 6,296,312; 6,403,312; 6,708,120; 6,792,356; PCT/US98/07254 and PCT/US01/40091. Such methods have been used to generate novel proteins with enhanced properties, see for example, U.S. Patent Nos. 6,682,923; 6,627,186; 6,514,729; and 6,746,853. See also, Steed et al, Science (2003), 301: 1895-1898,; Hayes et al., PNAS, 99 (25): 15926-15931, and Luo et al., Protein Science (2002), 11: 1218-1226, all previously submitted. Applicant also notes that the methodology described in these patents and scientific

publications is not limited to enzymes, but applies to therapeutic proteins as well as any other type of proteins.

In further support of utility, the utility of these methods are recognized by those of skill in the art as useful techniques. A number of third parties have recognized the value of these methods. For example, in the article "Proteins from Scratch" (DeGrado, Science (1997), 278:80-81, previously submitted, biochemistry professor William F. DeGrado of the University of Pennsylvania School of Medicine, a world-renowned expert in protein structure, folding and design, comments on the computational platform designed by Dahiyat and Mayo in Science (1997), 278:82-87. This platform is an earlier version of the computational platform that has evolved and is claimed herein. Dr. DeGrado states:

> Not long ago, it seemed inconceivable that proteins could be designed from scratch. Because each protein sequence has an astronomical number of potential confirmations, it appears that only an experimentalist with the evolutionary life span of Mother Nature could design a sequence capable of folding into a single, well-defined three dimensional structure. But now on page 82 of this issue, Dahiyat and Mayo describe a new approach that makes de novo protein design as easy as running a computer.

Dr. DeGrado further states (col 1, paragraph 3):

> Thus, the problem of de novo protein design reduced to two steps: selecting a desired tertiary structure and finding a sequence that would stabilize this fold. Dahiyat and Mayo have now mastered the second step with spectacular success. They have distilled the rules, insights and paradigms gleaned from two decades of experiments into a single computational algorithm...Thus the rules of ...computational methods for de novo design may now be sufficiently defined to allow the engineering of a variety of proteins.

Thus, as can be seen from the selections cited above in Dr. DeGrado's article, Dr. DeGrado is commenting on the usefulness of the general method. Thus, Applicants respectfully dispute the Examiner's statement that "the article by DeGrado relates to the specific compound, Zinc finger protein". Dr. DeGrado is specifically discussing the computational design of Mayo and Dahiyat, not just a zinc finger protein.

Furthermore, Applicants respectfully submit that the Examiner has misunderstood DeGrado by his reference to the quotation at page 80 citing "de novo design is best approached by simultaneously considering all of the side chains in the protein-unfortunately, a very high order combinatorial problem". It is this very paragraph that goes on to discuss Dayhiyat and Mayo's DEE theorem to "efficiently search through sequence and side chain rotamer space" (see column 3, page 80, last sentence of second full paragraph). Thus the DeGrado article articulates that the Dahiyat and Mayo solution, which forms the basis of the present claims, is in fact very useful in the field of combinatorial evaluation.

Further, in 2002, Dr. Jeffery G. Saven, a well-known expert in protein design, has recently published a review of the state of the art in combinatorial protein libraries (see, Saven, JG, Curr. Op.

Struct. Biol. (2002), 12:453-458, previously submitted, where he states at page 456, col. 1, 3rd paragraph, lines 6 – 13:

> Not only can combinatorial methods be used for discovery but also, more deeply, they can inform our understanding of protein properties by generating and assaying whole ensembles of sequences. Traditionally, advances in structural biology have come from examining the structures of naturally occurring proteins, but with combinatorial experiments, an enormous diversity of sequences can be generated at the control of the researcher.

Saven also states that

> Thus, methods for winnowing and focusing sequence space are a viral component of combinatorial protein design (see page 453, column 1, first paragraph) . . . Combinatorial methods are powerful tools for cases in which we have an incomplete understanding of molecular properties.

The Saven publication, while not prior art in the instant application, shows that it is known in the art that combinatorial library generation has "real world use". Thus, the discussions above regarding examples of actual utility by Applicant, as well as recognition to those skilled in the art of protein design and combinatorial library generation, meets the utility requirement under 35 USC § 101.

In addition, the Applicants respectfully draw the Examiner's attention to the requirements as further outlined in the Guidelines:

> Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong," even when there may be reason to believe that the assertion is not entirely accurate. Rather, Office personnel must determine if the assertion of utility is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is credible unless (a) the logic underlying the assertion is seriously flawed, or (b) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility.
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> * * *
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> . . . a prima facie showing [of no specific and substantial credible utility] must establish that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the applicant would be specific and substantial.

Thus, the burden is shifted to the Examiner. The Applicants respectfully submit that this burden has not been met, and the rejection should be withdrawn.

The arguments made above with respect to 35 USC §101 are equally applicable to the rejection under 35 USC §112, first paragraph. The techniques described in the recited methods have a specific and well-established utility, and one skilled in the art would know how to use the claimed invention, particularly as demonstrated in the patents and scientific articles discussed above.

Lack of Utility under §112, 1st Paragraph

As argued above, there is sufficient utility under both 35 U.S.C. §§ 101 and 112 to meet the statutory requirements, and this rejection should be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

Claim 1 is rejected under 35 U.S.C. 112, first paragraph for failing to comply with the written description requirement. In rejecting claim 1, the Examiner's position appears to be that the specification is enabling only for the design of enzymes (see page 5 of the final office action). The rejection is moot as applied to cancelled claim 1. Applicants respectfully submit that this rejection does not apply to newly added claims 19-32 for the following reasons.

The Applicants acknowledge the Examiner's statement that the specification is enabling for methods utilizing enzymes, but respectfully disagree that other types of proteins are not enabled.

As stated infra regarding utility, Applicant respectfully submits that the application is enabled by the examples where a molecule whose coordinates were input into a computer, heavy side chain atoms were selected within a 4 Angstrom sphere around four catalytic residues. These heavy side chain atoms defined the variable residue positions for which a primary library was calculated. A probability table (Table 3) was calculated from the top 1000 sequences in the list (again see Table 3). Table 3 shows the number of occurrences of each of the amino acids selected for each position (i.e., 5 variable positions and 25 floated positions). One skilled in the art would readily be capable of extrapolating these examples to a variety of protein systems with a variety of functions, particularly when read in light of the specification (e.g. see Specification page 7, line 27 to page 9, line 5; page 34, line 22 to page 35, line 12). Thus these examples also show enablement.

With respect to the scope of the enabling disclosure not commensurate with the scope provided in the Specification, there is disclosure of using a computational design program, and preferably PDA® technology as embodiments of the invention. See Specification at page 2, lines 1-3; page 7, lines 9-12; and page 14, line 30 to page 15, line 5. In addition, the examples provide further enabling disclosure to one skilled in the art to practice this invention. As stated previously, the methodology is not limited to a particular kind of protein, and one skilled in the art would not be led to believe that this method is limited to enzymes. The method of the present invention is not limited to enzymes, since the modifications may be done to any proteins, not just enzymes. The methodology has been successfully employed in many non-enzyme proteins, e.g., TNF, GCSF, Interferon, etc. The publications cited in the section addressing the 35 USC §101 show the diversity of proteins that may be used. In addition, the article by Dr. Saven shows that those skilled in the art do not limit proteins by type (such as enzymes). The methodologies apply to any type of protein. The methodology requires that coordinates of a target protein be input. There is nothing in the methodology that so limits it only to enzymes, and while the examples show

enzyme modifications, these examples are just that, examples of how the technology works. The specification provides support for the use of any protein that may be used in this method. One skilled in the art would understand that this method may be used on any protein and not just limited to enzymes.

The Examiner cites the DeGrado reference at page 80 (See Office Action, page 6, first full paragraph). Applicants have two points; first of all, the applicants are not designing a protein de novo, which is the subject of the DeGrado quote, but are inputting the coordinates of a target protein. Inputting the coordinates of a target protein is the equivalent to enabling the analysis of that particular protein structure. The methodology employs known physio-chemical parameters of proteins, amino acids and rotamers to modify the target protein. Secondly, DeGrado also actually discusses the fact that this "very high combinatorial problem" is addressed by the Dahiyat and Mayo technique. Thus, DeGrado also supports a finding of enablement of the present techniques.

Thus for every protein (not just enzymes), the same methodology as recited in the instant claims is used.

There is no undue experimentation since the specification enables one skilled in the art to practice the invention using the specifically recited steps in the claims. The Examiner refers to Cys, Pro and Gly not being used in an Example in the specification. Applicants' respectfully refer the Examiner to page 17, lines 30-35, where the specification discloses the basis behind using, or not using certain amino acids in certain situations. To one skilled in the art of protein design, this is not undue experimentation but a design choice. With respect to the Examiner's comments regarding SO2 and water being removed, Applicants' respectfully refer the Examiner to page 15, lines 6-25 for the discussion on backbone structure preparation, as well as the discussion on backbone preparation above.

Applicants respectfully point to In re Goffe, 191 USPQ429 (CCPA 1976), where the court stated:

> For all practical purposes, the Board would limit Appellant to claims involving the specific materials disclosed in the examples, so that a competitor seeking to avoid infringing the claims would merely have to follow the disclosure in the subsequently issued patent to find a substitute. However, to provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found to work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional propose of promoting progress in the useful arts.

Additionally, in In re Angstadt, 190 USPQ 214, 218 (CCPA 1976), the court further stated:

> Appellants have apparently not disclosed every catalyst which will work; they have apparently not disclosed every catalyst which will not work. The question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with every species covered by a claim. To

> require such a complete disclosure would apparently necessitate a patent application or applications with "thousands" of examples or the disclosure of "thousands" of catalysts along with information as to whether each exhibits catalytic behavior resulting in the production of hydroperoxides. More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed.

Therefore, in conclusion, Applicants submit that the Specification taken in conjunction with the state of the art at the time the invention was filed fully enables a person skilled in the art to practice the method of the invention without undue experimentation. Applicants respectfully request reconsideration and withdrawal of the rejection.

Applicants respectfully submit that the specification enables a method for computationally generating a genus of secondary libraries comprising variant sequences in which the starting protein structure (*i.e.* target protein or scaffold protein) can be any protein for which a three dimensional structure is known or can be generated. In addressing the written description requirement under 35 U.S.C. § 112, the Federal Circuit in University of *California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), stated:

> A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling with the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. This is analogous to enablement of a genus under Section 112, para. 1, by showing the enablement of a representative number of species within the genus. *See Angstadt*, 537 F.2d at 502-03 (deciding that applicants "are *not* required to disclose *every* species encompassed by their claims their claims even in an unpredictable art and that the disclosure of forty working examples sufficiently described subject matter of claims directed to a generic process) . . . See also *In re Grimme*, 274 F.2d, 949, 952 ("[I]t has been consistently held that the naming of one member of such a group is not, in itself, a proper basis for a claims to the entire group. However, it may not be necessary to enumerate a plurality of species if a genus is sufficiently identified in an application by other appropriate language.").

In support of the position that Applicants' have designed many proteins that are not "enzymes", Applicants enclose herewith a number of publications that are both prior and subsequent to the filing date of the present application. These are not offered to augment the disclosure of the application; rather, the work is presented to show that present invention is enabled for any protein for which a defined set of coordinates can be generated. *See In re Wilson*, 135 USPQ 442, 444 (CCPA 1962); *Ex parte Obukowicz*, 27 USPQ 2d 1063 (BPAI 1993); *Gould v. Quigg*, 3 USPQ 2d 1302,1305 (Fed. Cir. 1987):

> "it is true that a later dated publication cannot supplement an insufficient disclosure in a prior dated application to render it enabling. In this case the later dated publication was not offered as evidence for this purpose. Rather, it was offered . . . as evidence that the disclosed device would have been operative" printed publications.

For example, previously submitted articles describe computationally designed GCSF (US 6627186 and Luo P et al., Protein Science 11, 1218-1226 (2002), Interferon Beta (US 6514729) and TNF-alpha (US publication No. 2003/138401 and Steed PM et al, Science 301, 1895-1898 (2003); for example. These non-enzymatic proteins have a variety of structures and have all been successfully designed. Thus, it is improper to limit the scope of this invention to just "enzymes".

Applicant's respectfully point out the new claim 22 specifically recites PDA® in response to the Examiner's statement at page 6 first full paragraph of the Office Action. PDA is a preferred embodiment of Applicant's invention, but this particular computational approach is not necessarily required. Applicant's also respectfully dispute that the recited method claims are "the shot in the dark, genetic approach" (see Office Action, page 6, first full paragraph). The approach is rational, not random ("shot in the dark"). Applicant's again reiterate that one skilled in the art would be enabled to practice the steps of the method without undue experimentation.

The articles, patents and patent applications discussed above, support the enablement of the methods disclosed in the pending claims. Importantly, the methods apply to proteins in general, regardless of whether the protein is an enzyme, as described in the example, or an antibody, cell surface receptor, or other protein of interest.

Accordingly, Applicants respectfully submit that the specification fully enables the present claims, and respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 102

Claim 1 is rejected under 35 U.S.C. § 102(b) as being anticipated by Fechteler et al., 1995, *J. Mol. Biol.*, 13: 114-31. In rejecting claim 1, the Examiner's position appears to be that at page 128, that designing a protein model is the same concept as generating a second variant library, and thus, Fechteler describes the same computational method as taught in the instant application. The rejection is moot as applied to cancelled claim 1. Applicants respectfully submit that this rejection does not apply to newly added claims 19-32 for the following reasons.

To anticipate a claim under 35 U.S.C. § 102(b), a reference must teach every element of the rejected claim (MPEP § 2131).

Applicants respectfully submit that Fechteler teaches a method for predicting the three-dimensional structure in insertion /deletion regions of a protein structure that combines cluster analysis

with a geometric scoring criteria. Fechteler uses clustering with geometric criteria to narrow the list of fragment options when attempting to fit structural fragments onto the existing template structure. The modeling in Fechteler always takes place for a single unique protein sequence (i.e. although structural variants are created, no sequence variants are created).

Applicants also respectfully reiterate that Fechteler does not teach synthesis of proteins of the invention – the methods sections on pages 128-129 of the Fechteler reference merely spell out the details of the Fechteler structure prediction method, and the only entity that can be produced by the method of Fechteler is a theoretical list of 3-D coordinates for placement of atoms in space. Indeed, as Fechteler was completely focused on predicting the structure of a protein based on its sequence, the method was only applied to sequences that had already been synthesized and characterized – that is, the order of application is reversed relative to the Applicants' method in which variant sequence libraries are designed and then produced.

Further, the Fechteler reference does not create novel variant sequences. All of the sequences identified are the same as in the initial set.

In contrast to Fechteler, claims 19-32 use physico-chemical scoring functions (e.g. van der Waals, hydrogen bonding, etc.), probability tables and protein design automation to computationally filter variant protein sequences and generate a primary list of variant proteins. The current invention then further generates a secondary library of variant protein sequences by combining a plurality of variant amino acid residues. There is also no discussion or teaching in Fechteler of combining a plurality of their database fragments. Fechteler does not teach or suggest the use of scoring functions, probability tables, protein design automation, or the design of variant protein sequences and libraries.

Hence, Fechteler does not anticipate the claimed subject matter. Withdrawal of the rejection under 35 U.S.C. § 102(b) is requested.

Conclusion

Applicants respectfully assert that the present claims are in condition for immediate allowance. If an interview would expedite prosecution of the present application, the Examiner is invited to contact the undersigned at (415) 781-1989.

Respectfully submitted,
DORSEY & WHITNEY LLP

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By: _____
Timothy A. Worrall, Reg. No. 54,552 for
Robin M. Silva, Reg. No. 38,304
Filed under 37 C.F.R. § 1.34

555 California Street
San Francisco, California 94104-1513
Telephone: (415) 781-1989
Fax No. (415) 398-3249

Customer No. 32940